REMARKS

Claims 1 and 3-5 are pending in this application. Claims 6-15 have been added with this amendment. After entry of the above amendments and new claims, claims 1 and 3-15 will be pending. The above amendments introduce no new matter. Support for the amendment to claim 3 can be found throughout the application, for example at page 4, lines 9-14. Support for the amendment to claim 4 can be found throughout the application, for example at pages 15-16. Support for new claims 6 and 7 can be found, for example, at page 9, lines 24-30. Support for new claims 8 and 9 can be found, for example, at page 10, lines 1-5. Support for new claims 10-12 and 13-15 can be found, for example, at page 9, lines 30-37. Applicants respectfully note that the above amendments were made to facilitate prosecution and not in acquiescence to the Examiner's rejection. Applicants reserve the right to pursue subject matter deleted with this amendment at a later date.

Applicants gratefully acknowledge the Examiner's statement that rejections of record not reiterated in the present Office Action have been overcome. Applicants further gratefully acknowledge the Examiner's withdrawal, pursuant to 37 CFR 1.114, of the finality of the previous Office Action, and the Examiner's acknowledgement, pursuant to the obviousness-type double patenting rejection, of Applicant's intent to file a Terminal Disclaimer pending a finding of allowable subject matter.

Rejection under 35 U.S.C. §112, first paragraph (enablement)

The rejection of method claims 3 and 4 under 35 U.S.C. §112, first paragraph has been maintained because "the specification, while being enabling for methods of using the claimed compounds in cell culture, or to reduce some measures of immune stimulation, does not reasonably provide enablement for methods of treating mammals or methods of therapy using the instantly contemplated compounds." In response to Applicants arguments of record, the Office Action continues to assert that Applicants' claims are overly broad in "encompassing inhibiting any RNA target, in any disease related to aberrant gene expression in any mammal." Basically, the Office Action continues to maintain that Applicants' invention, providing

modified CpG-containing oligonucleotides with reduced immunostimulatory activity, is not enabled where there is evidence that antisense therapy is not always effective and/or free of side-effects. Applicants respectfully note that the Office Action does not cite claim 5 as rejected for lack of enablement, and, accordingly, Applicants presume that it has not been rejected on this basis.

In order to facilitate prosecution and not in acquiescence to this rejection, Applicants have amended claims 3 and 4, and added new claims 6-15. These amendments and new claims add no new matter. The location of support in the application as filed for these amendments and new claims is as described in detail above. Applicants' amendments are believed to obviate the remaining disputed grounds for rejection. In particular, Applicants have amended the claims to remove the disputed "modulating gene expression" and "therapeutically treating" terms. Applicants respectfully note that enablement is to be judged in view of the invention that is claimed, and the claimed invention here is critically aligned with Applicants' finding that certain types of oligonucleotide modifications beneficially avoid the immunostimulatory side effects of certain CpG-containing oligonucleotides. Applicants have thereby significantly advanced the state of the art of oligonucleotide therapeutics, and the invention, as now claimed, is clearly fully enabled to that end.

Accordingly, reconsideration and withdrawal of the rejection is respectfully requested.

Rejection under 35 U.S.C. §102(a)

The Office Action further states that the rejection of claim 1 under 35 U.S.C. § 102(a) as being anticipated by Krieg (WO/962555 or Krieg *et al.* (1996) Antisense & Nucleic Acid Drug Development 6: 133-9) is maintained. In particular, the Office Action states that, despite Applicant's amendment addressing the "inverted CpG" asserted to be taught by Krieg *et al.*, "Krieg continues to teach some of the remaining limitations, particularly....stereospecific phosphorothioate CpGs because "any phophorothioate linkage is sterospecific" (and) Krieg *et al.* teaches phosphorothioate linkages for the purpose of increasing the stability of immunostimulatory oligonucleotides.

Applicants respectfully traverse this rejection because the general teachings of CpG-containing oligonucleotides that also carry phosphorothioate backbone modifications neither technically describes, nor can legally anticipate, the "stereospecific phosphorothioate CpG's" of the invention.

As Applicants' specification teaches, CpG dinucleosides are, for the purposes of the invention, considered to be "unmodified" if the internucleoside linkage is a racemic phosphorothioate linkage (see page 8, lines 3-6), while such a CpG dinucleoside should be considered to be "modified" according to the invention if they are covalently linked to each other through a sterospecific phosphorothioate internucleoside linkage (see page 12, lines 23-35). Accordingly, the mere presence of a chiral center at the phosphorus atom of a phosphorothioate linkage does not provide for the corresponding stereospecific CpG centers of the instant claimed invention.

Indeed, the Krieg *et al.* references do not teach phosphorothioate CpG dinucleosides, let alone stereospecific phosphorothioate CpG dinucleosides. In particular, WO/96255 describes immunostimulatory oligonucleosides containing a CpG dinucleoside, which, in certain of their preferred embodiments, are also are rendered nuclease resistant by phosphorothioate modification of at least the terminal internucleotide linkages (see, for example, page 13, lines 21-24, and page 17, lines 26-31). Not only does the WO/9602555 reference does not specifically teach phosphorothioate linkages positioned particularly within CpG dinculeosides, but, further, the teachings of the Krieg *et al.* references are completely unlike those of the instant invention because they are directed toward immunostimulatory oligonucleotides, whereas the instant invention is directed toward modified oligonucleotides that avoid immuostimulatory activity. The non-specific phosphorothioate modifications taught by Krieg *et al.* are for the purpose of protecting the CpG-containing oligonucleotides against nuclease degradation so as to prolong the half-life of the oligonucleotide *in vivo* and thereby prolong the immunostimulatory effect. In contrast, the instant invention teaches stereospecific CpG linkages for the purposes of avoiding such immunostimulatory effects so as to reduce the immune side-effects of antisense administration.

Accordingly, the Krieg *et al.* references do not specifically provide for phosphorothiate CpG linkages, and, further, do not suggest making any such modifications that would lead to reduced immunostimulation.

Furthermore, the Krieg *et al.* references simply fail to teach the claimed stereospecific phosphorothioate CpG's. The mere presence of a latent chiral center in the phosphorothioates taught by Krieg *et al.* does not anticipate corresponding stereospecific isomers. Indeed, the Krieg *et al.* references do not mention stereospecificity in general, or stereospecific phosphorothioate CpG's in particular. Furthermore, the teachings of Krieg *et al.* would necessarily lead to the production of non-stereospecific phosphorothioate compounds that are racemic mixtures of the two possible stereoisomers. Accordingly, the Krieg *et al.* references simply do not teach stereospecific phosphorothioate CpG's. The courts have addressed the issue of whether a prior art teaching of a racemic mixture anticipates a claim to a corresponding stereospecific compound and have found that it does not (see *In re May and Eddy*, 574 F.2d 1082, 197 USPQ 601 (1978), holding that "the novelty of an optical isomer is not negated by the prior art disclosure of its racemate" (citing *In re Williams*, 171 F.2d 319, 320 (1948)).

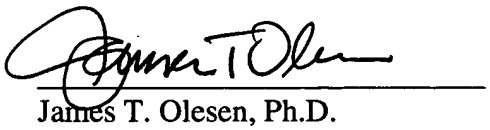
Therefore, the teachings of the Krieg *et al.* references do not anticipate the stereospecific phosphorothioate CpG's of the instant invention and, accordingly, reconsideration and withdrawal of the rejection is respectfully requested.

CONCLUSION

Applicant believes that the presently maintained rejections of the pending claims have been fully overcome by the amendment and arguments presented above. Accordingly, Applicant respectfully submits that the pending claims are in condition for allowance, and prompt acknowledgment of such is respectfully requested. If the Examiner believes that any further discussion of this communication would be helpful, he is encouraged to contact the undersigned by telephone.

The time for responding to this action has been extended to December 1, 2004 by the accompanying Petition for a Two Month Extension of Time and payment of fee. No additional fees are believed to be due in connection with this communication, however, please apply any additional charges, or credit any overpayment, to our Deposit Account No. 08-0219.

Respectfully submitted,



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